

إحتنا في المحاضرة السابقة تحدثنا عن الـ Absorption و الـ Distribution

في هذه المحاضرة نكمل باقي ال Pharmacokinetics و فاضلها تقسيم  
ال Metabolism و ال Excretion.

وتبدأ بال

# Metabolism

## Biotransformation

Most drugs will have a prolonged action if termination of their action depends only on renal excretion

يعني لو اعتمدنا على الـ *excretin* فقط في الهواء نضيّق الـ effect بتأثير طويل جداً  
فيكون هناك حاجة بتدخل اسمها *Metabol* هي التي بتوقف الـ effect بتأثير الهواء  
وتساهم على الـ *excretin* كلها

→ Lipophilic xenobiotics (foreign substances) are transformed or, metabolized in our bodies to a more polar substances. So, they get more readily excretable.

لحم البقر  $\rightarrow$  muscle  
excretory system

الإحابة:  $\text{cell membrane}$  إلى  $\text{tubules}$  إلى  $\text{polar}$  لما يوصل إلى  $\text{Kidney}$  إلى  $\text{cell membrane}$  إلى  $\text{reabsorption}$  على طريق  $\text{cell membrane}$  إلى  $\text{polar}$  ولأنه حاسة تدعى إلى  $\text{cell membrane}$  إلى  $\text{lipophilic}$  ترى ما قلنا المحاضرة إلى فانت في الحصة بتأت إلى  $\text{absorption}$  إلى فيها إلى  $\text{ionized}$  وإلى  $\text{non-ionized}$  وإلى  $\text{protonated}$  وإلى  $\text{non-protonated}$



- ⊗ Metabolic products are often less pharmacodynamically active than parent drug, may be even totally inactive as in what happen due to 1<sup>st</sup> pass effect.

طريق إيد الجسم بسم ال 1<sup>st</sup> pass effect و ال Metabolism الطبي ؟

ال 1<sup>st</sup> pass effect هو ال drug يعبر على ال liver ويحدث Metabolism قبل ما يدخل ال systemic circulation و بكرة يبقى طوي أي فاشة خالص

⊗ 1<sup>st</sup> pass effect : it's the Metabolism of drug in the 1<sup>st</sup> single passage after absorptn, before reaching the systemic circulation.

أما ال Metabolism الطبي يدخل ال drug بعد ما يعبر في ال systemic circulation و يدخل ال Body tissue و يعبر على ال liver و ال Metabolism الطبي و يخرج ال excretion و ال الطبيعي

- ⊗ Some Metabolic processes may enhance the drug activity or may reach toxicity.

- ⊗ Enzymes of drug Metabolism have been used in the design of pharmacologically inactive (prodrugs) that are converted to the active molecules in the human body.

- ⊗ Drug Metabolism passes through 2 phases in the human body

و تطلقا لثانوية كل phase يدخل فيها إيد .



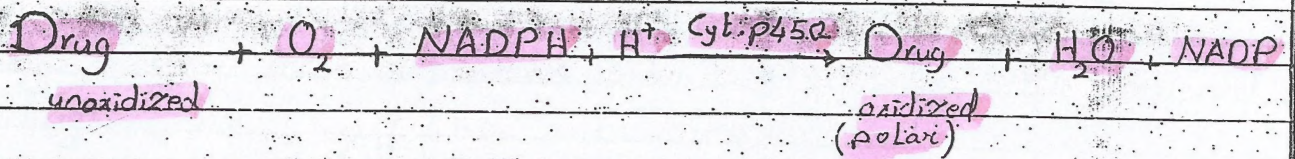
## Phase I

→ Convert lipophilic molecules into more polar molecules  
؟ (لجی)

By introducing or unmasking a polar functional group  
eg:  $\text{NH}_3^+$  or  $\text{OH}$  or  $\text{COOH}$

؟ و میم الی بیجی لک

→ This is catalyzed by the Cytochrome p450 system which is a microsomal mixed function oxidase



→ Cytochrome p450 contain many isoenzymes

Some drugs can induce or inhibit their synthesis

(\*) induced by :  
① Carbamazepine      ② Phenobarbital  
③ Phenytoin          ④ Rifampin

(\*) inhibited by :  
① Grape fruit Juice  
② Azole antifungals  
③ Cimetidine      ④ Erythromycin

(\*) Drugs Metabolized by Cyp450 :  
① antihistaminics  
② Ketoconazoles  
③ anti HIV protease inhibitors



إيه يا عم إنت كل الأسماء دي؟ هي علينا حفظ؟

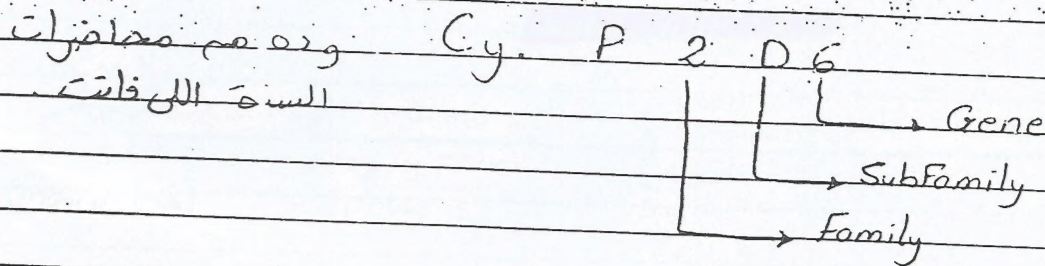
الإجابة: يا حفظ واحد أو اثنين مع كل واحدة لأنه الدكتور لم يركز عليها خالص لكن هم موجودين علينا.

\* Also the action of cytochromes p450 is affected by:

- ① Drug-drug interaction
- ② non-genetic factors eg: race differences
- ③ genetic factors eg: individual variance.

\* Some drugs are eliminated through Cy. p2D6  
 But they aren't common because 50% of clinically used drugs are Cy. p450 substrates.

وحدة كبر السيفري

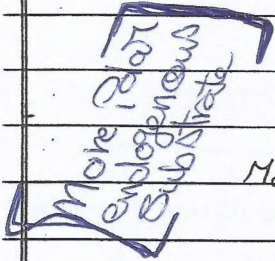


non polar drugs ال Phase I بيحول ال  
 cytochrome p450 syst ال Polar Subs.



## Phase II

- \* In this phase  $\rightarrow$  Subsequent conjugation with a more polar endogenous substrate occur as:
- Sulfuric, gluconic, acetic, amino acids.



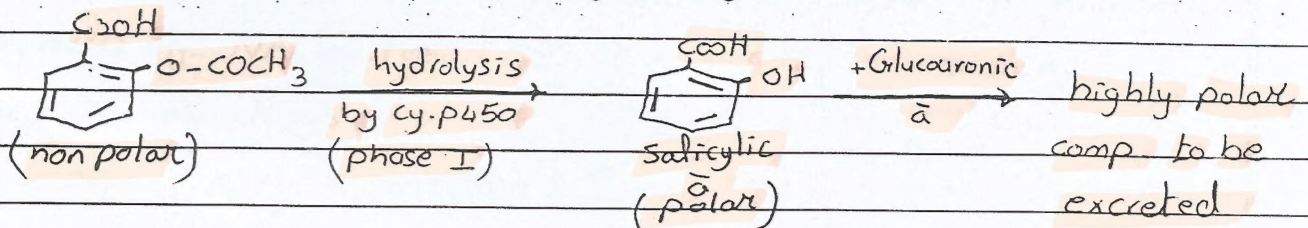
يجب المركب بناتي بزيادة قابلية في حالة تآكلية أكثر

- \* This result in more water sol. compounds that are therapeutically inactive (totally)

- \* Glucuronidation is the most common process.

Example for phase I, II on aspirin.

(acetyl salicylic a.)



بمراجعة ملحقتي أنقل  
المركب ده ولم أجده في أي مصدر سامعوني من أولو حكام نقله يعني يقول لي أنيق  
نزل المحاضرة القادمة

من كده إحنا خالصنا ال Metabolism  
من أعمالوا نشوف أهم حاجة في ال pharmacokinetics وهي ال excretion



⊛ all drugs pass through phase I then phase II of metabolism

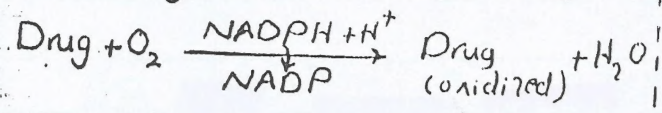
{except} isoniazide drug (INH) For T.B. treatment.  
 → it passes through phase II the phase I of metabolism.

### Liver enzymes responsible for metabolism.

\* Liver microsomal enzymes (LME)  
 or, Microsomal enzyme system.  
 or, Mixed function oxidases.  
 (Mono oxygenases)

Non microsomal enzyme system

NADPH-cytochrome P450 reductase



Cytochrome P450

لازم نقطة الـ points الـ  
 كويس اوى

\* very important in metabolism

by help of NADP-reductase it can carry out oxidatn, or, reductn, of drugs

\* contain many isoenzymes :

3	A	4
2	C	9
2	D	6
Family	Subfamily	Gene.

\* Most important isoenzyme is cytochrome 3A4 which is responsible for metabolism of 50% of drugs.

\* some drugs can induce these enzymes : ----- من الحافزة

\* " " " inhibit " " : ----- " "

\* They are affected by : Genetic, nonGenetic factors, Drug-drug interactn, ..

\* Drugs metabolized by cyt. P450 are : ----- من المعالجة



## Excretion

\* The Kidney is the most important excretory organ for drugs & their metabolites

\* Substances excreted in faeces are :

- a) unabsorbed orally ingested drugs
- or, b) drug metabolites coming out in bile or, secreted directly in intestinal tract, not reabsorbed.

\* Renal excretion involves 3 distinct processes :

① glomerular Filtration : Most drugs - unless bound to plasma proteins  $\rightarrow$  pass the glomerular filter freely

② Active proximal tubular Secretion : Many drugs as weak  $\text{a}^-$  weak bases are actively secreted in the renal tubule, thus more rapidly excreted

③ Passive distal tubular reabsorption : \* As drug moves towards distal tubule its conc increases, exceeds that of the perivascular space

o Lipid sol. (unionized) drugs passively reabsorbed by diffusion across the tubular membrane  $\rightarrow$  so not excreted in urine

$\rightarrow$  Because of pH partition, weak  $\text{a}^-$  are more excreted in Alkaline urine, Vice versa

وهذا الكلام الذي قلناه الحافضة الهامة  
في المسالك إلى حزام بنوع ال  
aspirin



فيها Math كثير  
كثير في الآخر متابع منها  
Pharma مهنة في الـ

## Renal elimination

نیقاع ال drug

Kidney II بحريّة

(Quantitative) اِیْلوس

→ plasma clearance is the volume of plasma from which all the drug appears to be removed in a given time (min).  
expressed as ml/min.

$$\text{Excretion rate} = \text{clearance} \times \text{plasma conc}$$

$$\text{mg/min} = \text{ml/min} \times \text{mg/ml}$$

→ when clearance is constant → Excretion rate  $\propto$  plasma conc.

⊗ total clearance of drug by several organs is additive

$$Cl_{total} = Cl_{hepatic} + Cl_{renal} + Cl_{pulmonary} + Cl_{others}$$

But It's impossible for us to measure, add these individual clearance to get the total clearance.

بہ نسبتوں کی آزادی؟

→ Total clearance can be derived from the steady state equation:

$$I_{\text{total}} = K_f \cdot V_d$$



\* Excretion Rate =  $\frac{\text{clearance}}{(\text{mL/min})} \times \text{plasma Conc. (mg/mL)}$

by steady state eq. \*  $\underset{\text{SS}}{Cl_{\text{total}}} = \underset{\substack{\uparrow \\ \text{elimination Rate Const. (clearance Const.)}}}{k_{\text{el}}} \cdot V_d \rightarrow \text{Vol. of distribtn} \Rightarrow \boxed{k_{\text{el}} = \frac{Cl_{\text{total}}}{V_d}}$

$\approx \infty$  most Drugs follow 1st order kinetics.

\*  $\infty C_t = C_0 - \exp^{-k_{\text{el}} t}$  [as elimination Rate Const.  $\propto$  drug Conc.]

$\ln C_t = \ln C_0 - k_{\text{el}} t$  at  $t_{1/2} \rightarrow C_t = \frac{1}{2} C_0$

$\infty \ln \frac{C_0}{2} = \ln C_0 - k_{\text{el}} t_{1/2}$

$\ln \frac{C_0}{2} - \ln C_0 = -k_{\text{el}} t_{1/2}$

$\ln \frac{C_0}{C_0 \times 2} = -k_{\text{el}} t_{1/2}$

$\ln \frac{1}{2} = -k_{\text{el}} t_{1/2}$

$\boxed{\ln 2 = k_{\text{el}} t_{1/2}}$

$\infty t_{1/2} = \frac{\ln 2}{k_{\text{el}}} = \frac{0.693}{k_{\text{el}}} = \frac{0.693}{\frac{Cl_{\text{total}}}{V_d}} = \frac{0.693 \cdot V_d}{Cl_{\text{total}}} \Rightarrow \boxed{\infty t_{1/2} = \frac{0.693 V_d}{Cl_{\text{total}}}}$

$t_{1/2} \propto V_d$

$t_{1/2} \propto \frac{1}{Cl_{\text{total}}}$



- \* Several important drugs are removed by renal excretion and are liable to cause toxicity in elderly people (Geriatrics), patients with renal diseases.

ومعظم الحقة دي

فيها Math كثير

لكم في الآمز كتلوع منها  
بمادة مهمة في ال Pharma

Quantitative aspects of

Renal elimination

يعني ال eliminata,

تفاع ال drug

ال kidney بطريقة

حسابية (Quantitative)

Clearance :

→ plasma clearance is the volume of plasma from which all the drug appears to be removed in a given time (min).  
expressed as ml/min.

$$\text{Excretion rate} = \text{clearance} \times \text{plasma conc.}$$

mg/min                      ml/min                      mg/ml

→ when clearance is constant → Excretion rate  $\propto$  plasma conc.

\* total clearance of drug by several organs is additive

$$Cl_{\text{total}} = Cl_{\text{hepatic}} + Cl_{\text{renal}} + Cl_{\text{pulmonary}} + Cl_{\text{others.}}$$

But It's impossible for us to measure, add these individual clearance to get the total clearance.

سبب كذا كذا

→ Total clearance can be derived from the steady state equation :

$$Cl_{\text{total}} = K_d \cdot V_d$$



where :  $cl_{total} \rightarrow$  total clearance ,  $V_d \rightarrow$  volume of distribution  
 $K_d \rightarrow$  constant of clearance (elimination rate const.)

طبيب احنا اوجبتا ال  $K_d$  بطريقة ما ، وعلنا ال  $V_d$   
 فنقدر نحسب ال  $cl_{total}$

من دلوقة احنا عايزين نحسب ال  $K_d$

⊗ Most drugs exhibit 1<sup>st</sup> order kinetics where the rate of elimination is  $\propto$  to drug conc.

taking this fact exponentially

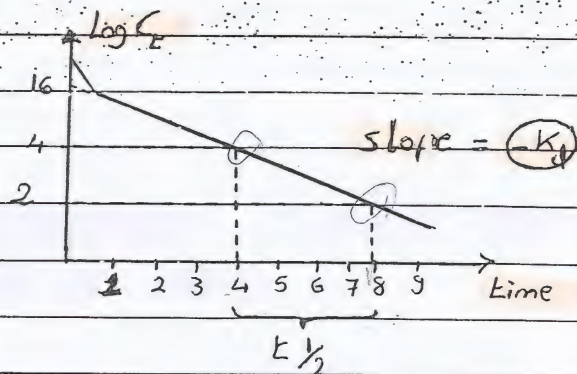
$$C_t = C_0 \cdot \exp^{-K_d t}$$

where :  $C_0 \rightarrow$  initial conc. of drug in plasma

$C_t \rightarrow$  conc. after elimination of some drug after time (t)

Plotting ( $\log C_t$ ) against (t)  $\rightarrow$  we get a straight line whose slope is  $-K_d$

$\rightarrow$  So we can easily calculate  $cl_{total} \rightarrow$  knowing  $V_d$



كده يا شباب انا عايزنا نحسب ال  $cl_{total}$  وعرفنا نحسب ال  $t_{1/2}$   
 مع ال graph  
 عايزين طريقة نحسب ايها ال  $t_{1/2}$  بطريقة Mathematically



From the equation  $C_t = C_0 \cdot \exp^{-K_d t}$   $\rightarrow$  (1)

$\rightarrow$  taking  $\ln \rightarrow \ln C_t = \ln C_0 - K_d t$   $\rightarrow$  (2)

$\rightarrow$  at  $t_{1/2} \rightarrow C_t = \frac{1}{2} C_0 \rightarrow$  (3)

$\therefore$  By substituting From (3) in (2)

$$\therefore \ln \frac{1}{2} C_0 = \ln C_0 - K_d t_{1/2}$$

$$\therefore \ln \frac{C_0}{2} - \ln C_0 = -K_d t_{1/2}$$

$$\therefore \ln \frac{C_0}{2} - \ln C_0 = -K_d t_{1/2}$$

$$\therefore \ln 0.5 = -K_d t_{1/2} \quad \therefore \ln 2 = K_d t_{1/2}$$

$$\therefore t_{1/2} = \frac{\ln 2}{K_d} = \frac{0.693}{K_d} = \frac{0.693}{\frac{Cl_{total}}{V_d}} = \frac{0.693 V_d}{Cl_{total}}$$

$t_{1/2} \rightarrow$  The half life of the drug  $t_{1/2}$  is the time taken for  $C_t$  to decrease by 50%

$t_{1/2} \rightarrow$  is inversely related to the clearance, directly prop. to the volume of distribution of the drug.



∴ the half life of a drug is increased by :

- ① ↓ clearance : (a) ↓ renal plasma flow  
(b) renal disease.  
(c) ↓ metabolism by enzyme inhibition.  
(d) Liver disease

- ② ↑  $V_d$  by another drug displacement.

كيفية تأثيره على الحمار والسيارة

في ذلك قانون آخر من كونه لوجهه في آخره وخلاصه

$$Cl_{\text{drug}} = Q \times E$$

(blood flow) (extraction ratio)

$$= Q \times \left[ \frac{C_A - C_V}{C_A} \right]$$

where  $C_A \rightarrow$  arterial end drug conc.  
 $C_V \rightarrow$  Vein end drug conc.



$$\begin{aligned}
 \text{Cl}_{\text{Drug}} &= \text{Q}_{\text{Blood flow}} \times \text{E}_{\text{Extraction Ratio}} \\
 &= \text{Q} \left[ \frac{C_A - C_V}{C_A} \right]
 \end{aligned}$$

$C_A \rightarrow$  Drug conc. in artery

$C_V \rightarrow$  " " " " vein -



∴ the half life of a drug is increased by :

- ① ↓ clearance ∴
- (a) ↓ renal plasma flow
  - (b) renal disease.
  - (c) ↓ metabolism by enzyme inhibition.
  - (d) Liver disease

② ↑  $V_d$  by another drug displacement.

که آن به نام الحار و سیه

منه ناله قاتله آخر من که لوحه من تعرفه و خلاص

$$Cl_{\text{drug}} = Q \times E$$

(blood flow)      (extraction ratio)

$$= Q \times \left[ \frac{C_A - C_V}{C_A} \right]$$

where  $C_A \rightarrow$  arterial end drug conc.  
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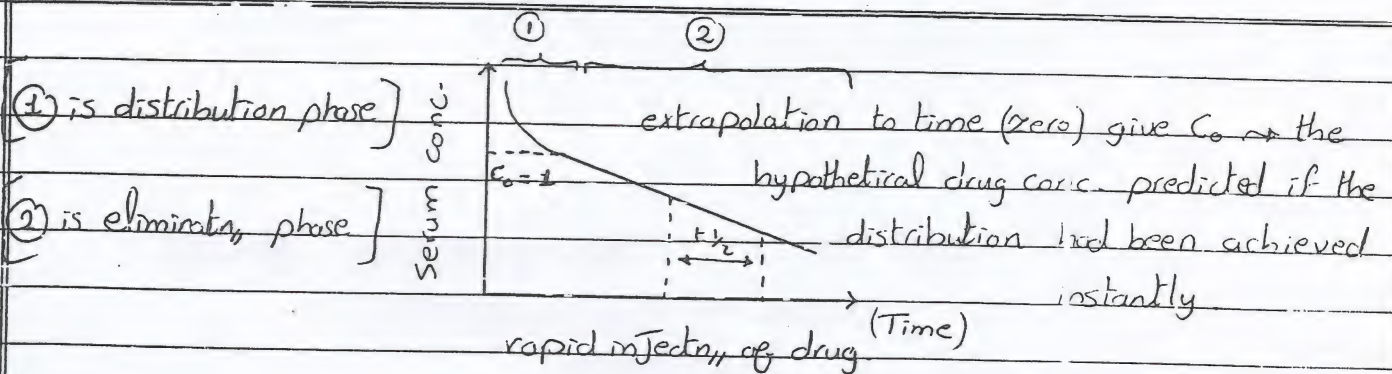
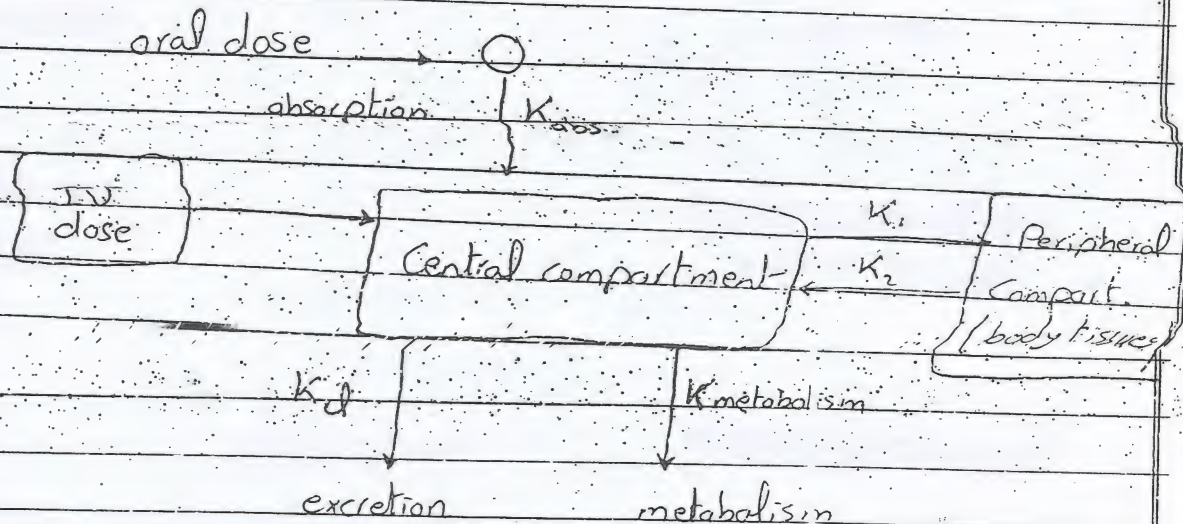
أنا في نفس من قام الصيغة

و مع آخر حدة في ال

# Pharmacokinetics

→ a 2 compartment model is often needed. in this case the kinetics is biexponential.

→ The 2 components roughly represents the processes of transfer between plasma & tissues [ $\alpha$ -phase] and elimination from plasma [ $\beta$ -phase]





# The Human Nervous System

**CNS** (central nervous syst.)

→ Brain & spinal cord

(Peripheral nervous syst.) **PNS**

→ neurons & ganglia outside Brain, spinal cord.

**Efferent** (motor)

neurons

output

جهاز CNS

**Afferent** (sensory)

neurons

input

**Somatic N.S.**

(Voluntary)

جهاز إرادي

**Autonomic N.S.**

(Involuntary)

جهاز لارادي

**Enteric**

**Sympathetic**

**Para sympathetic**

⊛ → Beside Nervous system → Endocrine system helps in Body Control i.e., regulatn, of homeostasis.

⊛ → A.N.S (autonomic N.S) works by

**Neurohormonal theory**

**Definition :**

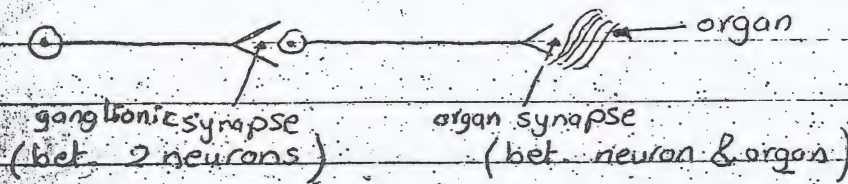
"it's the transmission of nerve impulse across a synapse by secretn, of a chemical neurotransmitter."



\* → A.N.S is faster in homeostasis regulatn, than Endocrine system as it acts on Both ganglionic synapse & organ synapse

يا عم انت كمال تقول لنا synapse هو مكان تفكرنا بيك ؟

→ Synapse is the Junctn, between any 2 neurons or, between a neuron & target organ



### Role of C.N.S. in A.N.S Activity

\* Although the A.N.S is a motor system, it requires a sensory input from peripheral structures to provide information on the state of affairs in the body.

مايك الفرق ده ؟

لازم ال A.N.S. يحيطه sensory input فاشه انه يقول لل A.N.S. حالة الجسم و ال A.N.S. تأخذ المعلومات ده و بيتنى يشتغل بحيث انه يضبط الجسم



\* These afferent (sensory) impulses originates from the Viscera, other organs then travel to integrating centres in the C.N.S as medulla oblongata, spinal cord, hypothalamus

\* These centres respond to stimuli by sending out efferent (motor) impulses via the A.N.S.

\* Emotions Can modify the activity of A.N.S  
fear pleasure rage

فهمنا أن العلاقة بين A.N.S و C.N.S

\* Reflex arcs (actions) → occurs in ganglia that are entirely outside the cerebrospinal axis for very rapid actions that doesn't need thinking or human consciousness at all.

كل الكلام الذي فات ده قديم ومعروف

→ تعاملوا بنا فركن سوية على ال A.N.S وندرس  
تفاصيله.



Autonomic Nervous

System (ANS)

OR

Visceral OR Vegetative OR Involuntary

\* From its name  $\rightarrow$  it's obvious that it controls the involuntary (unconscious) actions in the body.

\* It's distributed throughout the whole body.

\* In the periphery  $\rightarrow$  it consists of :

↓  
Ganglia

Aggregates of nerve cell  
bodies

↓  
Plexus

Aggregates of nerve cell  
Fibres (axons)

\* They innervate the heart, blood vessels, glands, visceral organs, smooth muscles.

كل الحاجات التي انت مش بتحكم فيها



# A.N.S. Anatomy, Ganglions, Fibres

-17-



\* الورقة دي لازم تقرأ وتكتب كل جزء جزء



وَمَعْلَى هَاطُولِ عَلَيْكُمْ وَهَاطُولِ الرِّسَالَةِ إِلَى فَاتِ حَتَّ حَتَّ

## ① Parasympathetic neurons.

(a) origin → They come out from the Cranium in brain, from sacral regions of spinal cord.

Cranio : III, VII, IX, X, Sacral : S<sub>2</sub>, 3, 4

(b) Pregang. nerve fibre → Long

(c) Postgang. nerve fibres → short

Cranium → Brain  
Sacral region → S-cord

(d) Ganglion position → very close to target organ

(e) Neurotransmitter at ganglion → Acetylcholine  
or, dil. Nicotine

(f) receptor at ganglion → cholinergic neuronal  
or, (N) → nicotinic neuronal  
neuronal means between neuron, neuron.

(g) Neurotransmitter at organ → Acetylcholine  
or, Muscarine

(h) receptor at organ → cholinergic musculine.  
or, (M) Muscarinic musculine



## ② Sympathetic neurons

(a) origin → They come out of thoraco-lumbar regions of the spinal cord (from  $T_1 \rightarrow L_3$ )

(b) Pregang. nerve fibres → short

(c) Postgang. nerve fibres → Long

Thoracic  
lumber

(d) Ganglion position → close to C.N.S.

(e) Neurotransmitter at ganglion → Acetylcholine  
or, dil. Nicotine

(f) receptor at ganglion → Cholinergic neuronal  
or, (N) nicotinic

(g) Neurotransmitter at organ → Generally it's  
N.E. (norepinephrine)

in case of renal vascular smooth muscles can be also  
dopamine beside N.E.

exception → at sweat gland → Acetylcholine is produced.  
instead of N.E.

(h) receptor at organ → Adrenergic

↙ ↘  
β α



Comparison الی قات مع تبقی Points ال ال  
parasymp. ال و symp. ال ال

### ③ Somatic neurons

\* it differs from A.N.S. in that  $\rightarrow$  it consists of 1 neuron coming out of the spinal cord, goes directly to target organ (skeletal muscles) with no ganglia in the middle

\* Neurotransmitter at organ  $\rightarrow$  Acetylcholine  
or, dit. Nicotine

\* receptors at organ  $\rightarrow$  cholinergic muscarine  
or, Nicotinic muscarine

**N.B.**  $\rightarrow$  The denervated skeletal muscle lacking Myogenic tone are paralyzed & atrophied.  
یعنی لو نزلت skeletal muscle و نزلت مینا ال nerve supply ال یحصلها حال و قوت

**But** smooth muscles, glands generally retain some level of spontaneous activity independent of intact innervation.  
نکته (و مینا) یحصل فی حالة smooth mus. ال glands



## ④ Enteric Nervous system

\* Although E.N.S is classified as a third division of the A.N.S., it's actually composed of components of sympathetic & Parasympathetic nervous systems, has a sensory nerve connectn.

\* It controls the processes of mixing, propulsion, absorptn, of nutrients in the GIT.

anatomy of A.N.S. ال كذا كذا  
Conglia ال, Neurotransmitters ال

و تعالوا بعد كذا نسوة مع بعض

## Physiology of the A.N.S

Sympathetic

Parasympathetic

They regulate the activities of the structures that Functions below the level of Consciousness



## a. Sympathetic

\* The symp. system + adrenal medulla secretion is known as sympathetic adrenal system.

\* This system can discharge as a unit during anger, fright, fright → when sympathetically innervated structures are over the entire body are affected.

→ يعني يستغل كله في نفس الوقت على كل الجسم  
منه على organ واحد بس

\* This system isn't essential for normal life. But, under stress it becomes essential.

- \* Its effect :
- ① ↑ heart rate
  - ② ↑ blood pressure
  - ③ mobilize energy stores of the body.
  - ④ ↑ blood flow to skeletal muscles
  - ⑤ ↓ " " " skin, internal organs
  - ⑥ Dilatation of pupils of eyes.
  - ⑦ " " Bronchioles
  - ⑧ RBCs comes out of spleen to circulation.



## ⑥ Parasympathetic

\* Parasympathetic system is organized mainly for discrete [individually distinct] & Localized discharge i.e., never discharge as one unit.

→ if it acts as one unit → undesirable symptoms are produced.  
organ على فليكن و organ على فليكن، أيضا (يعني) تاني

مما (في) الـ symp. sys. لا يـ فليكن و فليكن  
على الجسم كله مرة واحدة

\* it's required & essential for life  
i.e., for digestive processes, eliminat<sup>n</sup>, of wastes, conservation of energy, maintenance of organ function during periods of minimum activity.

\* It's known as Rest & Digest system.

\* It's effect :

- ① Lowers heart rate

- ② ↓ blood pressure

- ③ ↑ Gastrointestinal movement, secret<sup>n</sup>, & absorpt<sup>n</sup>,

- ④ protects Retina of eye from xss Light

- ⑤ empties the urinary bladder & rectum.



\* Important to know that in sympathetic, parasympathetic actions → there's a kind of physiological antagonism  
 effect ال بتاعهم عكس بعضي

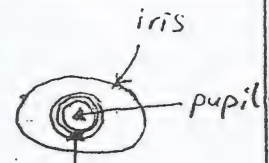
except in :

① Salivary glands → Parasymp. → ↑ secret<sub>n</sub>, → watery (profuse)  
 → Symp. → " " → viscid (sparse)

② Atrial conductivity from S.A. node of heart to A.V node → Parasymp. → ↑↑ atrial conduct.  
 → Symp. → ↑↑ " "  
 تعالوا لو ميني فاهمينها وأنا اشرحها لكم

③ Male genitalia → Parasymp → erection  
 → Symp. → ejaculat<sub>n</sub>.

Page (24) → Parasympathetic innervat<sub>n</sub>, only as constrictor (circular) pupile Muscles



those are the circular muscles

small blood vessels that contain non innervated Muscarinic receptors

يعني ايه ؟

يعني ال B.V. عليها Muscarinic receptors لكن ميني جاي لها neuron من ال A.N.S.

لكن أنا لو اديت رواد من هيمسك في ال receptor عادي جداً ويستغل كأنه جاء له impulse من ال parasympathetic system.



\* الحقائق دي مهمة جداً جداً ولازم تكون عارفها

→ we said that  $M_2, M_4$  work by  $G_i$  receptor of cAMP system.

→ add to them  $\alpha_2$  adrenergic receptor → it works in the same inhibitory mechanism.

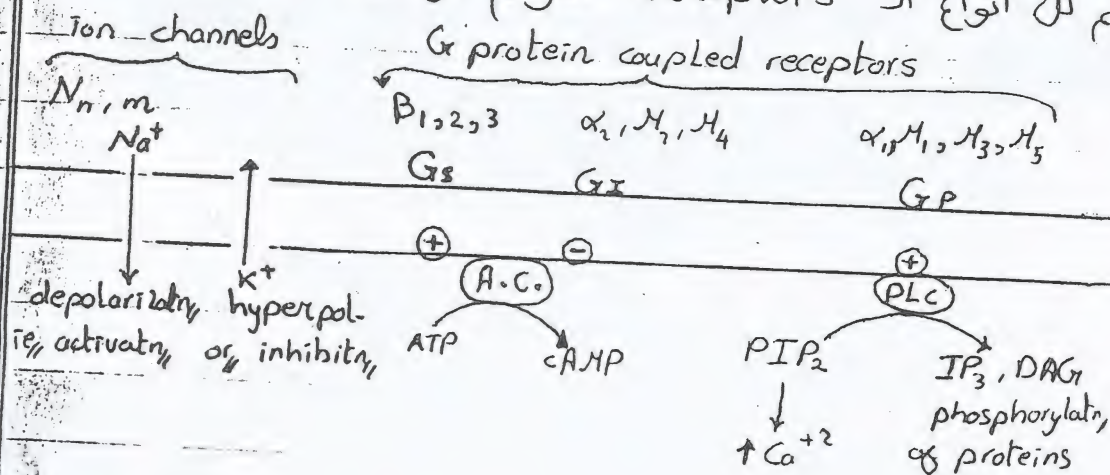
→ we said that  $G_s$  receptor works by increasing cAMP  
But we gave no examples.

examples : adrenergic  $\beta_1, \beta_2, \beta_3$  receptors

→ we said that  $M_1, M_3, M_5$  work by  $G_q$  → of Phosphatidyl inositol diphosphate system

→ add to them  $\alpha_1$  adrenergic receptor.

وعلى أساسه نعلم كل أنواع الـ receptors هتقسم إلى

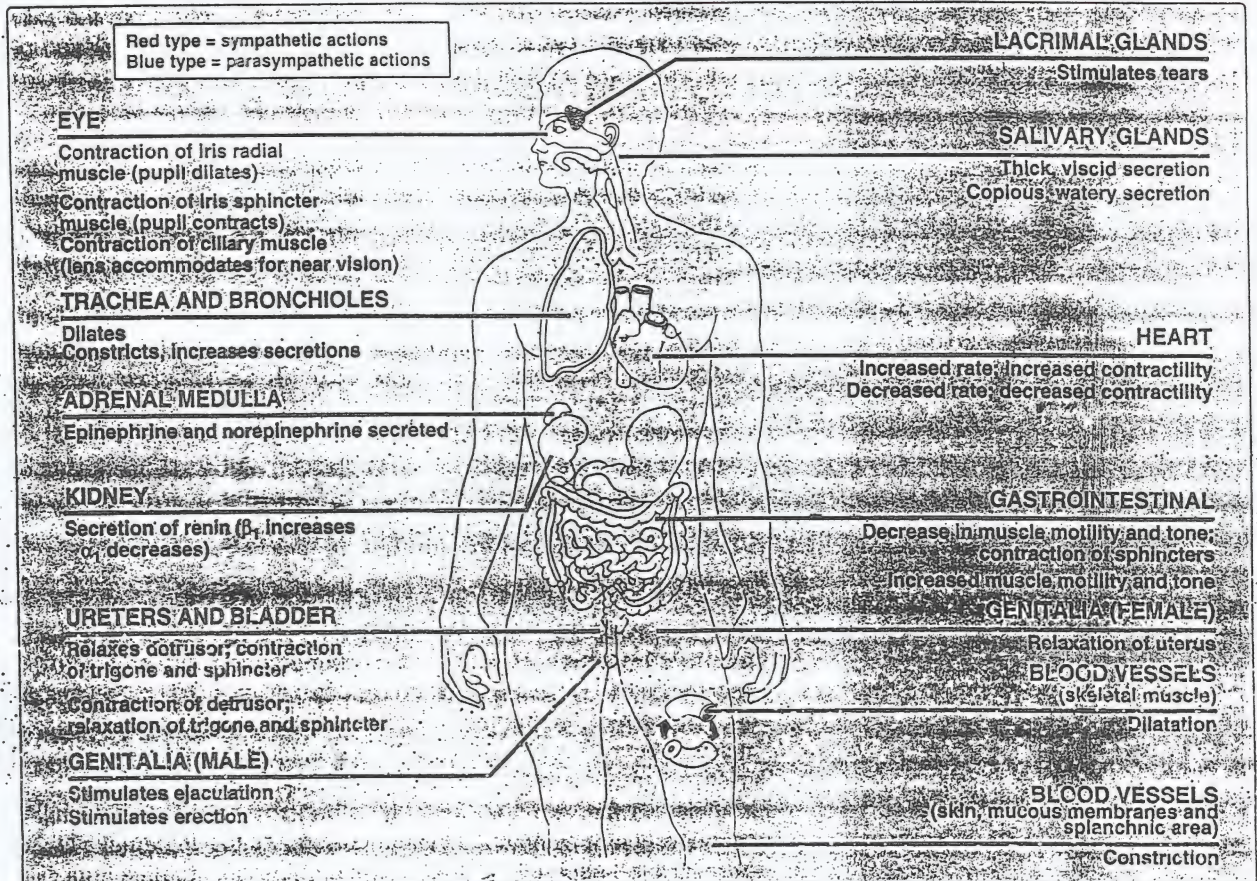




السمت الودي Sympathetic  
السمت القوي Parasymp.

## II. Introduction to the Nervous System

37





## Dual innervation

\* Most organs are innervated by both parts of A.N.S.

→ Symp →

→ Parasymp →

⬆

⬇

heart rate.

" " "

}

Give also

\* Despite the dual innervation → one system usually predominates in controlling the activity of a given organ.

for example :

in heart → the vagus nerve is the Predominant factor for controlling the rate.

\* only few organs receive only one kind of innervation.

Parasympathetic only	Sympathetic only
as constrictor pupile Muscles (circular Muscles)	as Dilator pupile Ms. (Radial Ms)
small Blood vessels contain non innervated Muscarinic receptors.	<ul style="list-style-type: none"> <li>- ventricles of heart.</li> <li>- Adrenal medulla</li> <li>- Sweat gland</li> <li>- Kidney</li> </ul>



# \* Neuro Transmitter Receptor \*

## Ion - Channel Coupled R

- R + Drug <sup>(N.T)</sup> Binding  $\rightarrow$

Polarizing state  $\rightarrow$  Depolarizing  $\rightarrow$

Rest  $\rightarrow$  hyperpolarization

\* Any out  $\uparrow$  +ve outside  
 $\downarrow$  -ve inside  
 or  $\uparrow$  -ve outside  
 $\uparrow$  +ve inside  
 (depolarization)

\* = =  $\uparrow$  +ve outside  
 $\downarrow$  -ve inside  
 (hyperpolarization)

Excitatory Agent

Inhibitory Agent

\* Cholinergic Nicotinic Receptors

## G-protein Coupled R

R + N.T  $\rightarrow$  2nd messenger

CAMP system

phosphorylation of serine & threonine of Protein

$\uparrow$  CAMP

$\uparrow$  Ca<sup>2+</sup> influx in heart  $\rightarrow$   $\uparrow$  Rate  
 $\downarrow$  kinase enzyme in smooth muscle  $\rightarrow$  relaxant

M2, M4 Receptors

Phospholipase C-system

acts on Phosphatidyl inositol Di-phosphate

IP<sub>3</sub> DAG

$\uparrow$  Ca<sup>2+</sup> from Endoplasmic Reticulum Contract  
 Phosphorylation & Cellular response

M1, M3, M5 Receptors

\* muscarinic R



تعالوا نتكلم شوية عن ال receptors ونسوف ايك انواعها  
وال Mechanism بتاعها بالتفصيل شوية عن المحاضرة الأولى

## Neurotransmitter Receptors

### Definition :

They are membrane proteins that provide a binding site that recognize and respond to neurotransmitter molecules.

### 4 Types :

- ① ion channel coupled receptor
- ② G protein " "
- ③ enzyme Linked "
- ④ receptors inside the cell

→ The most important 2 types to study now to know the mechanism of cholinergic , Adrinergetic receptors are :

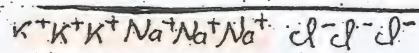
- ion channel coupled receptor.
- G protein " "





net -ve charge

Depolarization  
(excited) state

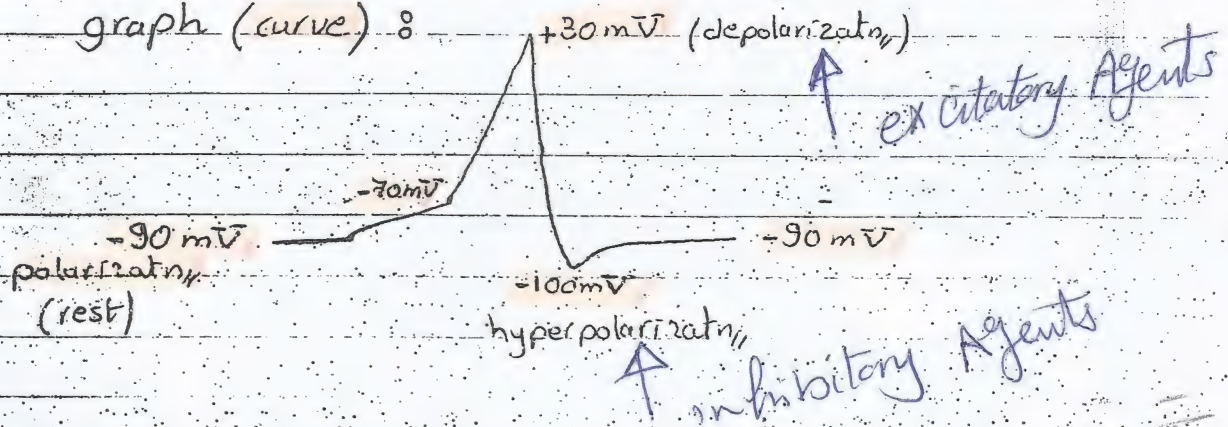


net +ve charge

→ This process occurs in milli sec.

→ Then the membrane returns to its rest (polarization) state by  $K^+$  efflux followed by  $Na^+ K^+$  pump.

→ The whole process can be represented as a graph (curve) :



→ From the curve we can conclude :

① any substance that decreases +ve charge outside or, decreases -ve charge inside can lead to depolarization, ∴ it's considered as excitatory agent.

② any Sub. that increases +ve charge outside ( $K^+$  efflux) or, increases +ve charge inside ( $Cl^-$  influx) can cause hyperpolarization, ∴ it's considered as inhibitory agent.



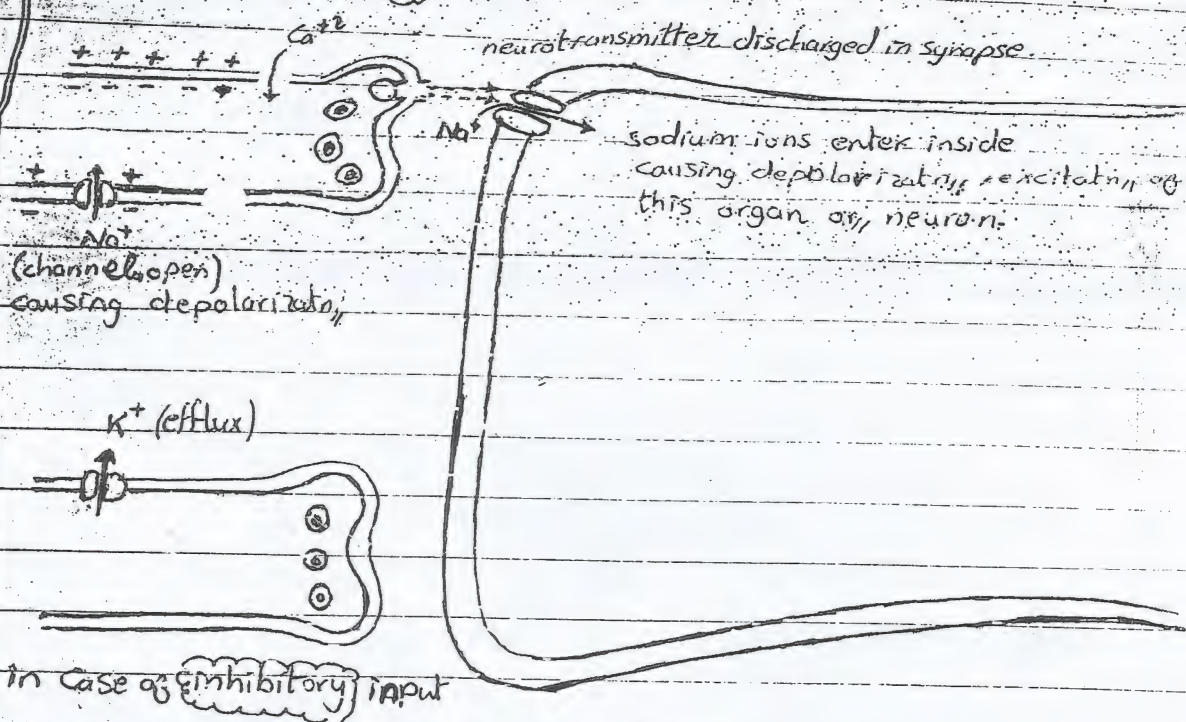
Receptors working using this Mechanism are:

## Cholinergic Nicotinic receptors

- which are present at:
- ① all ganglionic receptors
  - ② somatic Neuromuscular Junction,
  - ③ synapse at sweat glands of sympathetic innervation.

والرسمة التي جانبها الدكتور هي في حالة من

in case of excitatory input



K<sup>+</sup> efflux causes hyperpolarization, causing inhibition.

كده احنا خلاصنا ال ion channel coupled receptor  
 وبقا نعالو نسوف النوع الثاني وهو ال G protein coupled receptor



## ② G Protein Coupled Receptors

\* Binding of chemical neurotrans. to receptors activate enzymatic processes within the cell membrane that ultimately result in cellular changes such as phosphorylation of intracellular proteins.

\* Neurotransmitter  $\rightarrow$  Signal  
Receptor  $\rightarrow$  Signal detector & transducer

\* "Second messenger" molecules are produced in response to neurotransmitter binding to the receptor, translate the extracellular signal into a response  $\rightarrow$  propagated, amplified within the cell.

\* The most widely known Second messengers are:

- ① adenylyl cyclase system.
- ② Calcium / phosphatidyl inositol system.

تعالوا نسرح كل system فيہم بیشتر ازای

Phosphatidyl inositol  
Adenylyl Cyclase

Second messenger

- Adenylyl Cyclase
- Calcium / Phosphatidyl



## (a) Adenyl cyclase System

or, cAMP System

### (\*) Types of $\alpha$ protein :

- ①  $\alpha_s \rightarrow$  stimulatory  $\rightarrow \uparrow$  cAMP
- ②  $\alpha_i \rightarrow$  inhibitory  $\rightarrow \downarrow$  cAMP

### Role of cAMP

It induces phosphorylation of proteins at serine, threonine residues.

#### Cardiac muscle

phosphorylation process induces the activation of  $Ca^{+2}$  channels with  $Ca^{+2}$  influx causing  $\uparrow$  cardiac properties i.e., contraction, force, rate.

#### $\uparrow$ cAMP

#### Smooth muscle

phosphorylation process induces the inactivation of Myosin like chain Kinase enzyme causing  $\downarrow$  in smooth muscle contraction, i.e., causes relaxation.

هذا النظام يتصلب الـ Receptors الى سقالة الـ System  
Adrenergic و cholinergic و الـ موجوده فيه و الـ

$\uparrow$  cAMP



\* This kind of receptors working by this mechanism are :

cholinergic ; Muscarinic  $\rightarrow$  kind  $M_2, M_4$   
present in heart muscle , smooth muscle

هل حالة  $M_2, M_4$  هي التي يتبعها الأرقام دي ؟  
موسكارينيك كلها خلاص ؟

Answer :  $\rightarrow$  No, in mammals there are 5 distinct types of muscarinic receptors  
 $M_1, M_2, M_3, M_4, M_5$

$\rightarrow M_2, M_4 \rightarrow$  present in Cardiac Muscles, Smooth muscles  
work by cAMP system

But you have to know that when agonist bind to these  $M_2, M_4$  receptors  $\rightarrow G_i$  (inhibitory) is the one which acts  $\rightarrow$  decreasing cAMP causing cardiac muscle relaxatn, & smooth muscle contractn.

$\rightarrow M_1, M_3, M_5$  work by another system which is Calcium / phosphatidylinositol system or Phospholipase C system

وتعالوا نفوف ال system ده بيشتغل لازي



(b) Calcium/Phosphatidyl inositol  
diphosphate system

or, Phospholipase C system

\* Binding of Agonist to muscarinic ACH receptors ( $mACHR_s$ ) of type 1, 3, 5 ( $M_1, M_3, M_5$ ) activates phospholipase C enzyme

\* Phospholipase C enzyme causes hydrolysis of Phosphatidyl inositol 4,5 diphosphate into 8

① Diacyl glycerol (DAG)

② Inositol triphosphate ( $IP_3$ )

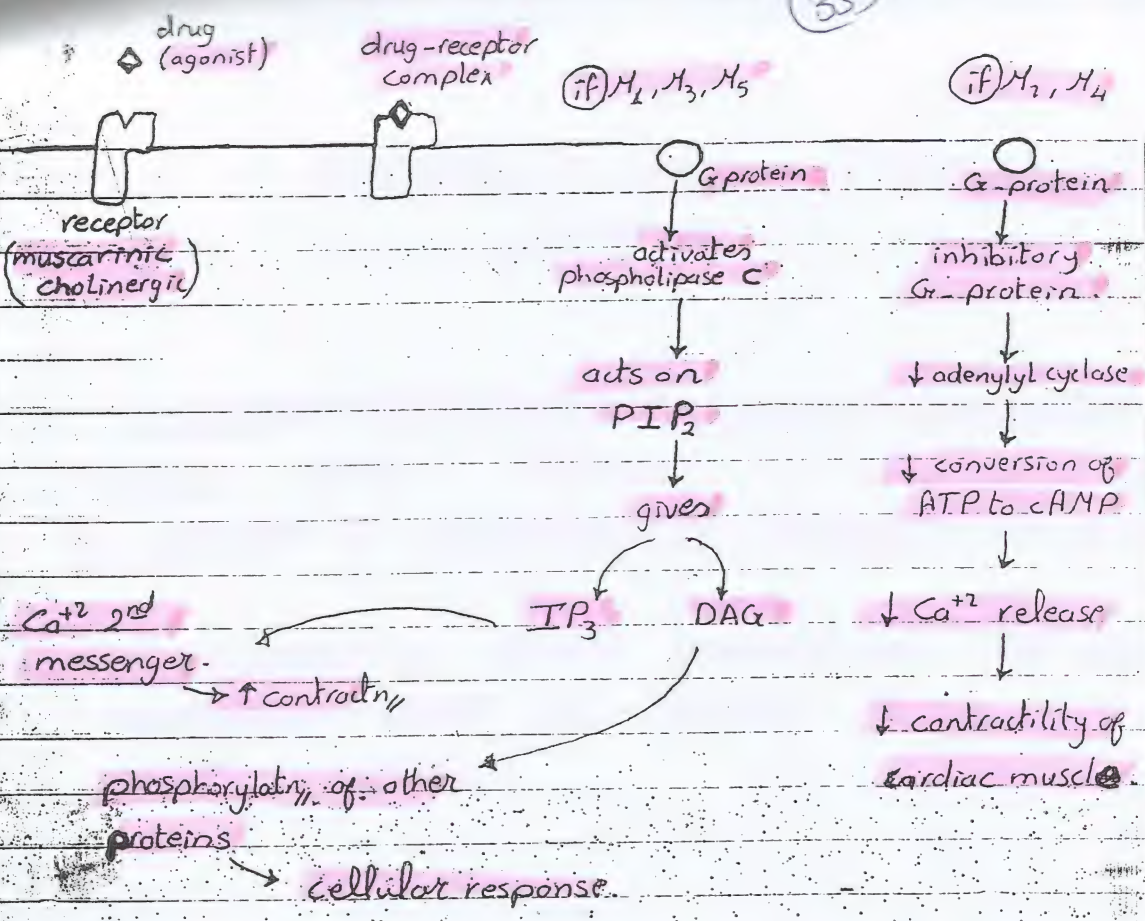
\*  $IP_3$  causes the release of intracellular  $Ca^{+2}$  ions from endoplasmic reticulum causing the action of  $Ca^{+2}$  dependant phenomena as muscle contraction.

\* DAG activates protein Kinase enzyme causing phosphorylation of numerous proteins leading to various physiological responses.

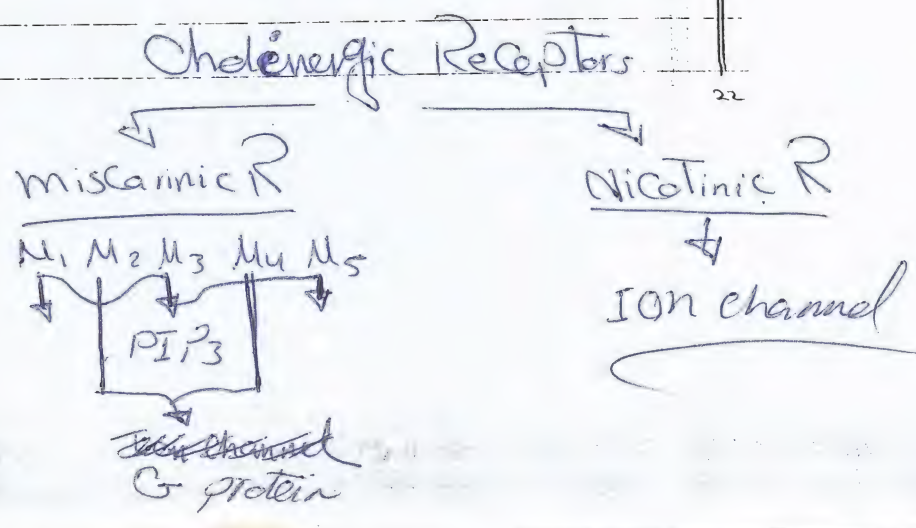
وعلامة نلاحظها في ال 2 systems الى فاقوا بوع ال  
muscarinic cholinergic receptors

منزلة الرسالة الى جاية دي





مستقبلات المسكارينية muscarinic receptors  
 Ca/phosphatidyl inositol triphosphate  
 ion channel  
 Nicotinic receptors  
 cholinergic receptors  
 Adrenergic receptors  
 Mechanism





## Molecular Basis of Adrenoreceptors Function

\* all of Adrenergic receptors are  $\alpha$ -Protein coupled Receptors ( $\alpha$ PCRs) where  $\alpha$ -protein is linked to heterotrimeric subunits ( $\alpha, \beta, \gamma$ )

\*  $\alpha$  proteins are signal transducers that convey information from the receptor to one or more effector molecules



وآخر حاجة فنتعرف على جود مسأله فإلى على الـ

والحقبة معروفين مسأله احسنه مسأله

اعرفوا مسأله الحاجات المميزه في

الـ heart والـ eye والـ GIT

كله بياض

## The Main Effects of ANS

Organ	Sympathetic effect	Adrenergic receptor type	Parasympathetic effect	Cholinergic receptor type
1. Heart	Rate ↑	$\beta_1$	Rate ↓	$M_2$
2. Atrial node	Force ↑	$\beta_1$	Force ↓	$M_2$
3. Atrioventricular node	Automaticity ↑	$\beta_1$	Conduction velocity ↓	$M_2$
4. Ventricular muscle	~	$\beta_1$	arterioventricular block	$M_2$
5. Coronary artery	constriction, dilatation	$\alpha_1, \alpha_2, \beta_2$	vasodilatation	due to EDHF
6. Muscle	Dilatation	$\beta_2$	-	(NO) release
7. Skin	constriction	$\alpha_1$	-	in response
8. Brain	constriction	$\alpha_1$	-	stimulation of non innervated $H_3$ receptors
9. Intestine	Constriction	$\alpha$	dilatation	$H_3$ [NO]
10. Salivary gland	constriction	$\alpha$	~	$M_3$
11. Vein	~	$\alpha$	activation of NO synthase	$H_3$
12. GIT:				
a) Smooth muscle	motility ↓	$\alpha_2, \beta$	Motility ↑	$H_3$
b) Sphincters	constriction	$\alpha_1$	Relaxation	$H_3$
c) Glands	secretion ↓	$\alpha_2$	Secretion ↑	$M_3$
			Gastric & secretion	$M_1$
13. Uterus:				
a) pregnant	contraction	$\alpha_1$	variable	$M_3$
b) non pregnant	Relaxation	$\beta_2$		



14. Male sex organ	Ejaculation	$\alpha_1$	erection	M <sub>3</sub>
15. Eye:				
a) pupil	dilatation (contraction of radial muscle of iris) "mydriasis"	$\alpha_1$	contraction of circular muscle causing constriction "miosis"	M <sub>3</sub>
b) Ciliary muscle	relaxation (slight)	$\beta_2$	Contraction	M <sub>3</sub>
16. Skin:				
a) sweat gland	sec. (mainly cholinergic)	$\alpha_1$	No effect	M
b) pilomotor	piloerection	$\alpha_1$	No effect	—
c) sweat	secretion (thick)	$\alpha_1$	secretion (watery)	M <sub>3</sub>
17. Liver	glycogenolysis gluconeogenesis	$\alpha_1, \beta_2$	No effect	—
18. Adrenal medulla	secretion of Adrenaline and nor Ad. [No sympathetic innervation]			N
19. Fat cells	Lipolysis	$\beta_3$	—	—
20. Urinary bl.:				
a) detrusor m.	relaxation	$\beta_2$	contraction	M <sub>3</sub>
b) trigone & sphincter	contraction	$\alpha_1$	relaxation	M <sub>3</sub>

Pray 4 us a lot ooooo



\* inhibits  $M_1 R$   $\rightarrow$  Pirenzepine

\*  $\sim$   $Nn R$   $\rightarrow$  hexamethonium

\*  $\sim$   $Nm R$   $\rightarrow$  d-tubocurarine

\* Cholinomimetics  $\rightarrow$  ACh - methacholine - Carbachol - Bethanechol  
 $\rightarrow$  muscarine, pilocarpine  $\downarrow$  selective  $M R$   
Nicotine, lobeline

\* DMPP  $\rightarrow$  Dimethyl phenyl piperazine  $\simeq$  nicotine